## REMARKS

With entry of this amendment, claims 16, 18-20, 36 and 41-45 are under examination. The claims have been amended to remove trademarked composition names. No new matter has been added. Reconsideration is requested.

A "Notice of Non-compliant Amendment" attached to the advisory action issued March 22, 2010 indicated that the status identifiers for claims 46-48 were incorrect. The status identifiers have been changed in accordance with the Examiner's comments.

**Claims amendment and 35 USC § 112, second paragraph rejection**

The claims have been amended to overcome 35 USC 112, second paragraph, rejections. Trademarked composition names have been deleted, and a generic description provided. Withdrawal of the rejection is requested.

**The invention**

Before addressing each rejection in more detail, a review of the invention and the conditions of its genesis should be made.

It has already been disclosed and discussed how the invention was obtained, thanks to a novel process.

What the novel process has achieved is a formulation that is (i) a tablet, (ii) with a bioavailability higher than the standard Lipanthyl®200M. This latter product corresponds to the product obtained with the Curtet reference, abundantly discussed in the specification through reference to the European counterpart (EP'532). Lipenthyl® has been used for the first and second generation products. The indication of "M" following the trademark indicates that this is the second generation product, which is co-micronized (hence the "M").

The invention allows an even lower dose, compared to the 200 mg of Lipanthyl®200M, thanks to an improved bioavailability, but with the same therapeutic effect. One will keep in mind that the standard Lipanthyl® can be delivered in either one strength of 200 mg or one strength of 67 mg (three times a day, thus the same daily dosage of 200 mg), corresponding to the second generation of Lipanthyl® products. This is in correspondence with the first generation product where the amounts were respectively 300 mg and 100 mg (Lipanthyl®300 and Lipanthyl®100, where the daily dose was 300 mg). Where it is indicated that the dosage

forms contain less than 200 mg, and with a bioavailability increased with respect to the Lipanthyl®200M, this means that compared to the strength of 200 mg of the prior art, the invention provides the same therapeutic effect with a lower amount of drug. Typically, an amount of 160 mg for the new tablet formulation provides plasma levels equivalent to those previously achieved by the Lipanthyl®200M; the daily dose is thus reduced from 200 mg to 160 mg.

For Lipanthyl®67M, an amount of 67 mg is lower than 200 mg, but (1) the daily dose remains at 200 mg (because the 67 mg strength is taken three times) and (2) the bioavailability is the one of Lipanthyl®200M. Lipanthyl® exhibits the same bioavailability for the 67 mg and the 200 mg strengths. A capsule of Lipanthyl® 67mg (apart from the fact that it is not a tablet) will not fall under the scope of the claim as presently pending.

The superior bioavailability was indicated in the Guichard reference ("A New Formulation of Fenofibrate: Suprabioavailable Tablets," Current Medical Research & Opinion, Vol. 16, No. 2, 2000, pp.134-138.), submitted with the prior response. Reference is made to the disclosure of the Guichard reference in the prior response.

Thus, there is ample showing of the superiority of the superbioavailable tablet of the invention.

Superbioavailability is also shown in table 1 (below) which lists $C_{max}$, $t_{max}$, $t_{1/2}$, $AUC_{0-t}$, $AUC_{0-\infty}$ as possible parameters, the last two being collectively referred to as "AUC" ($AUC_{0-t}$, $AUC_{0-\infty}$, sometimes also referred simply as $AUC_t$ and $AUC_\infty$ are the Area Under the plasma Curve from administration to last observed concentration at time t and extrapolated to infinite time, respectively). Claim 41 is directed to two parameters, AUC and $C_{max}$, useful for the assessment of bioavailability. Two main criteria are used when determining bioavailability (and subsequently bioequivalence), which are AUC and $C_{max}$, Area Under Curve and peak concentration, respectively. These two criteria are the main technical features, as can be seen from the extract of the two previously filed documents from the USFDA (Attachments A and B from the Amendment filed July 23, 2008). These two documents, albeit having a date which is after the priority date of the instant application represent what the skilled addressee would have understood at the time of filing. In both documents, AUC and Cmax are the two main characteristics. See especially the document entitled "*Guidance for Industry, Bioequivalence*

*Guidance*", page 2 which discloses "*AUC and CMAX as the pivotal parameters for bioequivalence determination*". See also especially the document "*Statistical Approaches to Establishing Bioequivalence*", at page 2. The skilled man would also consider the corresponding EU regulations, as evidence by the attached document issue by EMEA, entitled "*Note for Guidance on the Investigation of bioavailability and Bioequivalence*", especially at section 3.6.2. No new matter is added. One will keep in mind that the indication of the method for measuring

| Product | Dose (mg) | Cmax (µg/ml) | AUC 0-t (µg.h/ml) | AUC 0-∞ (µg.h/ml) |
|---|---|---|---|---|
| Invention | 200 | 5.4 | 148 | 162 |
| Lipanthyl® 200M | 200 | 1.6 | 71 | 92 |
| Ratio | 1 | 337% | 208% | 176% |

This is a showing that the bioavailability is greater than that of Lipanthyl®200M.

It is respectfully submitted that the feature "bioavailability being greater than that of 200 mg co-micronized fenofinobrate" does impart patentability. The greater bioavailability flows from a comparison between values for given groups of patients. It is a given that it is not permitted to compare two pharmacokinetics studies (PK studies) between them. It is only permitted to run one PK with two drugs and compare the results within one PK study. Values for AUC, Cmax, etc. need not be provided as absolute values; these values will vary form one group of patients to another. What is important is to make a comparison with the reference. This is what has been done in the present patent application which contains data from a PK study, where a comparison can be made. For an exemplary illustration of PK, one may revert to the Deboeck reference, and consider table at col. 8 (reproduced below in the section dedicated to the rejections). In this table, the same drug is given in a PK study, with two different conditions. AUC and Cmax are assessed; depending on the conditions, the results are different: for example the example 2 composition provides an AUC value of 181 and 107. The skilled man is well aware that it is not possible to compare results of two different PK studies. Thus, the AUC and Cmax values, for example, are representative of measurements of the bioavailability, which is assessed in one PK study (to be performed).

Also, it cannot be concluded that the claims are generic with respect to the parameters. The parameters are recited in the claims (part of them) to indicate the way the bioavailability is measured. Giving absolute values for the parameters would have no technical signification for the skilled man, as was shown above.

**35 USC §103 Rejections**

All claims under examination stand rejected as being obvious over Krause in view of Deboeck or alternatively over Ghebre-Sellassie in view of Krause and further in view of Deboeck. These rejections are traversed for the following reasons.

Krause is directed to compositions comprising fenofibrate and an ACAT inhibitor. Krause indicated that the compositions may comprise from 300 to 1200 mg of fenofibrate. Given the date of Krause, this obviously corresponds to Lipanthyl®300, the first fenofibrate product generation; this also flows from the lack of indication of micronization for the active ingredient fenofibrate, which is thus presumed to be present under the non-micronized state (typical particle size would then be 50-200μm). Examples directed to immediate-release tablets, i.e. examples 5-10, all use at least 300 mg of fenofibrate. The process for making the tablets is a standard wet-granulation technique, which is a standard technique distinct from the new process used of the invention. To conclude, the Krause tablets are at best bioequivalent to the Lipanthyl®300, the first generation of fenofibrate drugs. As a point of distinction, the Krause tablets are not even bioequivalent to Lipanthyl®200M, let alone superior to them.

Ghebre-Sellassie is directed to gemfibrozil and not to fenofibrate. Ghebre-Sellassie is directed to a specific embodiment where the tablet will have both an immediate-release fraction and a sustained-release fraction, obtained thanks to two different granulations. The granulation technique used for the immediate-release fraction (the first granulation in Ghebre-Sellassie) is a conventional wet granulation technique. What has been said above with respect to Krause can also be stated for Ghebre-Sellassie, since there is no indication of particle size and since the date of Ghebre-Sellassie is contemporary to Krause. Ghebre-Sellassie also uses an amount of hydrophilic polymer (see at col. 2, first paragraph and example 1) which is low. 6.4 parts of cellulosic polymer is used together with 255.5 parts of active, i.e. about 2.5%. This amount should be compared to that used in the invention, which is unusually high. The amount of drug that is used in Ghebre-Sellassie is not indicated in terms of amount per dosage unit. To conclude

on Ghebre-Sellassie, the tablets disclosed are even farther remote from the invention when compared to Krause.

Krause and Ghebre-Sellassie at best disclose a formulation that would be, in terms of bioavailability, at best comparable to the first generation, Lipanthyl®300.

This first remark is an important point to keep in mind. Krause and Ghebre-Sellassie correspond at best to the first generation of Lipanthyl® products.

Thus, the daily dose required in these two references is necessarily 300 mg.

Deboeck is directed to fenofibrate composition, and more specifically to a generic of Lipanthyl®200M. Indeed, column 8 referred to by the Examiner discloses (see table) fed and fasted bioequivalency tests between the Deboeck composition and Lipanthyl®200M. Note that Lipenthyl®200M is to be administered under fed conditions (i.e. at the time of the meal of shortly thereafter) and the fed conditions appear more appropriate for a comparison. It flows from the date given, notably AUC and $C_{max}$, (181 v. 184. 7 and 11.1 v. 10.9, respectively) that the Deboeck composition is bioequivalent to Lipanthyl®200M. Thus, Deboeck discloses a composition which has the same bioavailability as Lipanthyl®200M, i.e. to the second generation product. Further, Deboeck is directed to capsules and not to a tablet (the Deboeck formulations simply cannot be processed into tablets). When Deboeck indicates at col. 3, lines 36-38, that the composition offers an improved bioavailability with respect to conventional formulations, the conventional formulations are the first generation Lipanthyl®. A second generation Lipanthyl® has an improved bioavailability with respect to the first generation, but one should keep in mind what the "conventional formulation"' is referred to in Deboeck; it is not the Lipanthyl®200M (but rather the 300 mg formulation, first generation).

If one runs a comparison between the invention and Deboeck, the following can be concluded. One will consider the data obtained under fed conditions and fasted conditions.

Deboeck fed

| Product | Dose (mg) | Cmax (µg/ml) | AUC 0-t (µg.h/ml) | AUC 0-∞ (µg.h/ml) |
|---|---|---|---|---|
| Deboeck | 200 | 11.1 | 181 | - |
| Lipanthyl® 200M | 200 | 10.9 | 184.7 | - |
| Ratio | 1 | about 1 | about 1 | - |

Deboeck fasted

| Product | Dose (mg) | Cmax (µg/ml) | AUC 0-t (µg.h/ml) | AUC 0-∞ (µg.h/ml) |
|---|---|---|---|---|
| Deboeck | 200 | 5.1 | 107 | - |
| Lipanthyl® 200M | 200 | 5.9 | 101 | - |
| Ratio | 1 | about 1 | about 1 | - |

Thus, Deboeck provides a composition which has substantially the same bioavailability as that of Lipanthyl®200M.

Thus, the daily dose required in the Deboeck reference is necessarily 200 mg, when the standard is the Lipanthyl®200M. Lowering the dose in Deboeck will results in lower plasma level with the same bioavailability when compared to Lipanthyl®200M. A reduction of the dose in Deboeck is not concomitant with an increase in bioavailability.

The invention is directed to a composition which has a bioavailability that is greater than that of Lipanthyl®200M. Krause and Ghebre-Sellassie provide tablets having a bioavailability that is lesser than that of Lipanthyl®200M. Deboeck provides capsules having the same bioavailability as Lipanthyl®200M. Thus, none of the documents, either individually or in combination render the instant invention obvious. The invention is directed to (i) fenofibrate tablets which are (ii) suprabioavailable when compared to Lipanthyl®200M.

Indeed, the invention provides a composition having a bioavailability which is greater than that of Lipanthyl®200M. See the table below.

Invention

| Product | Dose (mg) | Cmax (µg/ml) | AUC 0-t (µg.h/ml) | AUC 0-∞ (µg.h/ml) |
|---|---|---|---|---|
| Invention | 200 | 5.4 | 148 | 162 |
| Lipanthyl® 200M | 200 | 1.6 | 71 | 92 |
| Ratio | 1 | 337% | 208% | 176% |

Because the bioavailability is enhanced, a lesser amount of drug will be needed to achieve the same therapeutic level. Thus, for the same therapeutic level, the daily dosage is lower than 200 mg while at the same time offering a bioavailability greater than that of Lipanthyl®200M.

The Examiner states that:

> "there is no patentability seen in Applicant's limitation of "wherein the bioavailability is greater than that of Lipanthyl®200M", since the prior art vividly teaches fenofibrate compositions having improved bioavailability; the same objective as that desired by Applicant."

This appears to be erroneous. Indeed, as demonstrated above, the prior art aims at achieving the same bioavailability of Lipanthyl®200M.

Further, the Guichard document should be considered. It can be concluded from this document (see figure 1) that the fenofibrate (which has a poor solubility) of Lipanthyl®200M dissolves in 120 minutes. This time corresponds about to the GI residence time (which is in general of about 3 hours); meaning that the sink conditions existing in the intestines would dissolve 100% of the drug: 100% of the drug would thus be available. If one considers document Guichard, fig. 1, then the skilled man can conclude the following. The curve denoted with ◊ corresponds to the Lipanthyl300mg, not micronized. The curve denoted with ■ corresponds to Lipanthyl®200M, co-micronized, subject of the invention of Curtet and taken as a reference in the invention (and also in Deboeck). The curve denoted with ▲ corresponds to the invention. The ◊ curve to the non-micronized product hardly achieves 70% at the end of the study (dissolution medium is not the one as used in the invention). At 60 minutes the ■ curve

(Lipenthyl®200M) achieves already almost 100% dissolution. At the end of the 120 minutes period the dissolution is 100%. If one compares these two curves, one will immediately understand that the non-micronized fenofibrate composition is dissolved at 70%, while the Lipanthyl®200M) is dissolved at 100%. Higher dissolution provides enhanced bioavailability: Lipanthyl®200M contains 200 mg while the non-micronized form contains 300 mg: 70% of 300 mg (which is dissolved at 70%) corresponds to 200 mg dissolved at 100%. Enhanced bioavailability was achieved with the Lipanthyl®200M because of higher final dissolution value, obtained with increased dissolution rate. The skilled man would thus conclude that the Lipanthyl®200M, which has been solubilised to 100% in 120 minutes, would be taken through the intestine mucosa and completely circulated into the body. The skilled man would conclude that the Lipanthyl®200M achieves the highest bioavailability.

Surprisingly, the invention demonstrates that it is further possible to increase the bioavailability of the fenofibrate compositions. This is further achieved with a tablet, compared to the Deboeck prior art which uses a capsule.

For all of the above reasons, it is respectfully submitted that the presently claimed invention is not obvious in view of the cited prior art. Reconsideration and withdrawal of the rejection is respectfully requested.

All rejections having been addressed, it is respectfully submitted that this application is in condition for allowance, and Notice to that effect is respectfully requested.

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Respectfully submitted,

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